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REVIEW ARTICLE

Mac-2 Binding Protein Glycosylation Isomer as a Marker of Hepatocellular Carcinoma in Patients with Hepatitis C Virus

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ABSTRACT

In chronic liver disorders, evaluation of hepatic fibrosis is essential. The glycosylation isomer of Mac-2 binding protein (M2BPGi) is a novel blood marker for liver fibrosis that can predict the development and prognosis of hepatocellular carcinoma (HCC), in addition to hepatic fibrosis in individuals with chronic liver diseases, such as persistent hepatitis C virus (HCV). In patients with cirrhosis, M2BPGi can also assess liver function and prognosis. The etiology and the presence or lack of treatment affects M2BPGi levels. Consequently, the background and treatment status must be taken into account while establishing the M2BPGi for the diagnosis of hepatic fibrosis and the prediction of HCC development. This review aims to assess value of M2BPGi as a predictor of HCC in HCV patients. This review concludes that M2BPGi can predict HCC in a wider range of patient populations including those with severe hepatic fibrosis.

Keywords: M2BPGi; HCC; Cirrhosis

INTRODUCTION

Glycoproteins are one of the main types of proteins found in the human body. They are proteins with glycan branching on their surface. Its branching shape and sugar composition are known to be highly specific to cell pathogenic alterations or differentiation stages. Thus, it has already been utilized in laboratory tests such as Hemoglobin A1c for measuring blood sugar levels or transferrin low in carbohydrates for prolonged alcohol consumption, as glycoprotein-based biomarkers (glycol-biomarkers) [1].

The degree and severity can offer crucial information for predicting the course of a patient's disease. Diagnosing liver fibrosis is still best done with a conventional liver biopsy. The liver biopsy is an invasive procedure and causes discomfort to the patient, it cannot be performed frequently. Furthermore, a variety of non-invasive scoring methods based on elastographic or serum marker procedures has been proposed as alternatives [2].

M2BPGI is one of the blood biomarkers for liver fibrosis that was just commercially released and introduced into labs. After being discovered in 2013 and used therapeutically as a Glycosylation isomer of serum Mac-2 binding protein as a diagnostic sign for liver fibrosis (M2BPGI) is being extensively utilized, primarily in Asia. Due to its simplicity of detection in the serum, M2BPGI has seen a sharp rise in clinical application in recent years. Its measurement has been used to evaluate the risk of carcinogenesis and liver fibrosis in chronic liver disorders [3].

M2BPGi and its characteristics:

The glycoprotein known as Mac-2 binding protein glycosylation isomer (M2BPGi) is generated by hepatic stellate cells (HSCs). In order to encourage fibrogenesis, it acts as a mediator between HSCs and Kupffer cells [4].

According to Narimatsu [1], M2BP's particular glycan structures alter as liver fibrosis worsens. The idea of M2BPGi measurement is to test M2BP with a modified glycan structure in order to assess liver fibrosis. Wisteria Floribunda Agglutinin, the lectin (WFA) was used to detect the change in the M2BP glycan structure, and it was discovered that this alteration was connected with the development of fibromatosis.

Mac-2 binding protein is produced by hepatocytes among other cell types, and its utility as a biomarker is based on modifications when considering its glycosylation pattern in relation to liver disease [5].

Utility of M2BPGi in chronic liver diseases:

Figure (1) illustrates the clinical utility of M2BPGi in chronic liver disorders. As the illness worsens, M2BPGi levels rise. When a chronic liver disease progresses, M2BPGi can be used to evaluate various aspects of the disease, including liver function, hepatocellular carcinoma (HCC) risk, recurrence risk, and liver fibrosis [6].

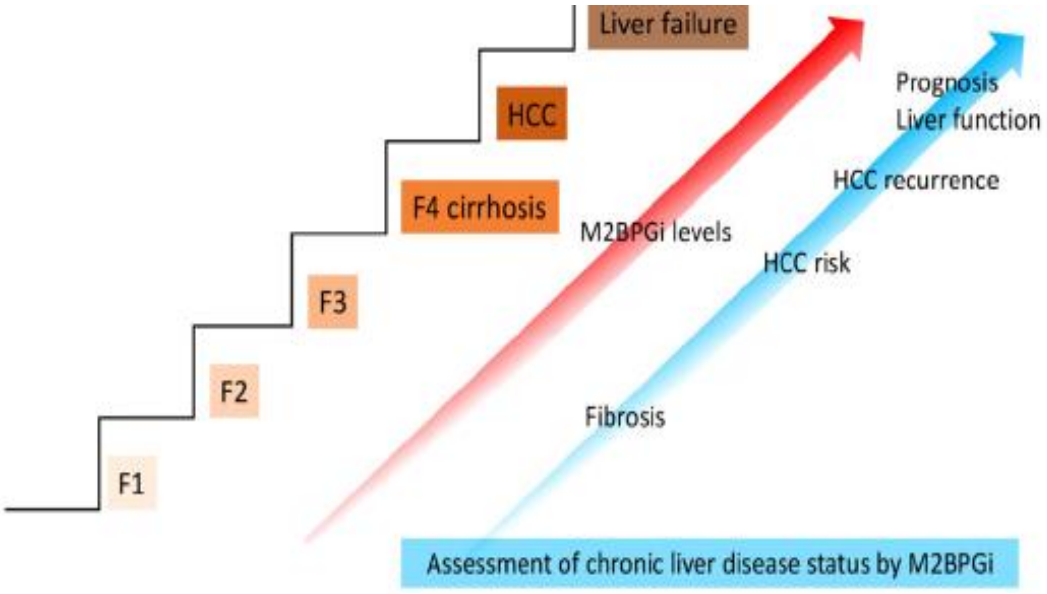

Figure (1): Clinical utility of M2BPGi in chronic liver diseases. The M2BPGi levels increase as the disease progresses from minimal liver fibrosis to decompensated cirrhosis. M2BPGi can be used to assess disease status such as liver fibrosis, HCC risk, HCC recurrence risk, liver function, and prognosis of chronic liver diseases, with the progression of the disease [6].

Abbreviations: M2BPGi, Mac-2 binding protein glycosylation isomer; HCC, hepatocellular carcinoma.

M2BPGi level predicts liver fibrosis and carcinogenesis in chronic hepatitis C:

The chronic hepatitis serum C (HCV) patients was utilized to generate the biomarker M2BPGi, which is currently routinely used to diagnose liver fibrosis in HCV patients [7].

In order to determine the stage of liver fibrosis, Nakamura et al. [8] contrasted the M2BPGi's diagnostic accuracy with a liver biopsy's. At stages of histopathological fibrosis 1, 2, 3, and 4, the mean COI values of M2BPGi were, in that order, 0.88–2.23, 1.81–3.86, 2.3–3.53, and 3.12–7.86.

The usefulness of M2BPGi for identifying liver fibrosis in HCV was validated by the fact that in every case, M2BPGi levels increased markedly as liver fibrosis developed. One of the risk factors for HCV carcinogenesis is liver fibrosis. As a result, M2BPGi forecasts the

emergence of HCC. M2BPGi ≥4.0 denoted an increased chance of developing HCC [9].

The ease of measurement and repeatability of M2BPGi is another benefit. An increase in HCC risk was linked to a gradual rise in M2BPGi levels. The prognosis for HCV is likewise correlated with high M2BPGi levels [10]. Additionally, Ito et al [11] verified the effectiveness of M2BPGi in fibrosis diagnosis and HCC risk prediction.

Utility of M2BPGi in chronic hepatitis C after sustained virologic response (SVR):

With direct-acting antiviral (DAA) therapy, SVR was attained in a number of patients. M2BPGi has a mild correlation with alanine transaminase (ALT) and inflammation in addition to a substantial correlation with liver fibrosis. As a result, M2BPGi rapidly drops with DAA treatment in accordance with an improvement in ALT levels or inflammation. Acute liver damage also causes an increase in M2BPGi [12].

Because of the enhanced inflammation, it is necessary to adjust the M2BPGi threshold for predicting the emergence of HCC after SVR. Research on the possibility of developing HCC following sustained viral remission (SVR) revealed a carcinogenic risk based on the M2BPGi value at SVR of 1.0–2.0, which was lower than that during chronic HCV infection [13].

Utility of M2BPGi in chronic hepatitis B:

When individuals' chronic liver disease progress, liver fibrosis HBV, M2BPGi levels rise. In the first four phases of histological fibrosis, the mean M2BPGi COI values are 0.26-0.9, 0.34-1.36, 0.57-1.65, and 1.21-3.1, in that order. Compared to patients with chronic HCV, M2BPGi was considerably lower in patients with chronic HBV. Consequently, taking into account the etiology of liver fibrosis, it is imperative to modify the M2BPGi threshold for hepatic fibrosis diagnosis [14].

When evaluating the likelihood of cancer development, treatment should be taken into account. When given nucleotide/nucleoside analogs (NA), M2BPGi level falls. As a result, while assessing M2BPGi level during NA treatment, the threshold must be lowered because M2BPGi level falls as fibrosis and inflammation heal. M2BPGi level ≥1.2 during NA treatment is linked to the prognosis and carcinogenesis of chronic HBV, and it is often lower than in those that have not had treatment [14].

Utility of M2BPGi in cirrhosis:

When compensated cirrhosis develops into decompensated cirrhosis, the M2BPGi level rises. Consequently, elevated M2BPGi levels in cirrhosis patients suggest a dismal prognosis. According to reports, M2BPGi can be used as a prognostic marker for problems and liver failure following transcatheter arterial chemoembolization or hepatectomy. Consequently, liver function as well as liver fibrosis are reflected in M2BPGi level. M2BPGi level can be used for follow-up following HCC therapy and is also linked to prognosis and recurrence following hepatoblastomy [15].

The complication of cirrhosis that has drawn attention is sarcopenia. M2BPGi level is a helpful prognostic marker for sarcopenia and is linked with muscle mass. Because it correlates with cirrhosis complications and prognosis, M2BPGi level is helpful for patients with cirrhosis [16].

Aside from viral hepatitis and non-alcoholic fatty liver disease (NAFLD), M2BPGi level can be useful in identifying liver fibrosis in cases of primary biliary cholangitis, autoimmune hepatitis, and biliary atresia, and primary sclerosing cholangitis [17]. However, there are few relevant research in this area.

Hepatitis patients' Mac-2 binding protein glycosylation isomer as a predictor for hepatocellular carcinoma C virus:

Yamasaki et al. [18] found that just 17% of the 707 Japanese patients with HCV had F4 fibrosis at baseline. Similarly, only 10.1% of the patients studied by Sasaki et al. [19] had baseline F4 fibrosis. Yamasaki within every stage of fibrosis, including F4 et al. [18] and Sasaki et al. [19] employed M2BPGi to assign a risk score for HCC.

Bekki et al. [20] shown that M2BPGi is produced in vitro by hepatic stellate cells and that the interaction of M2BPGi between Kupffer cells and hepatic stellate cells may induce a fibrogenic pathway in cells. There needs to be more investigation of the effects of underlying liver disease on M2BPGi performance. With varying ideal threshold values for each, M2BPGi has been demonstrated to be indicative of HCC in cohorts from East Asia with HCV, HBV, and NAFLD.

Jun et al. [21] found that M2BPGi levels were significantly greater in HCC patients than in non-HCC patients. No difference in M2BPGi levels was observed when the presence or absence of HCC was assessed after the fibrosis stages were adjusted, which was thought to reflect its carcinogenic potential due to fibrosis progression.

Bekki et al. [20] discovered that hepatocytes, Kupffer cells, endothelial cells, biliary epithelial cells, and hepatic stellate cells are among the subpopulations of liver-derived cells (HSCs), are the source of M2BPGi. Exogenous M2BPGi was reported to increase Mac-2 (galectin 3) expression by Kupffer cells in an in vitro research. Additionally, HSCs express more alpha-SMA in cocultures with Kupffer cells than do Kupffer cells, a phenomenon that is counteracted by Mac-2 removal from cells Kupffer. According to these findings, M2BPGi functions as a juxtacrine acting messenger that is transferred from HSCs to Kupffer cells in the course of liver fibrosis, and that it is crucial to the development of fibrosis. Therefore, unlike collagen content, M2BPGi levels indicate the HSCs' activity during the progression of liver fibrosis. This could explain the rapid decrease in M2BPGi levels that happens in patients with hepatitis C who have a prolonged viral response (SVR).

According to an immunohistochemistry examination of cirrhotic human liver, CD68-positive cells, likely Kupffer cells, express Mac-2 (galectin 3) and M2BPGi. In order to cause biological activity, M2BPGi may interact with Mac-2-positive cells. Mac-2 is involved in a number of different processes, including immunological responses, T cell death, cytokine synthesis, growth regulation, and cell adhesion. For instance, Kianoush et al. [22] propose that Mac-2 causes macrophage M2 polarization, and other research suggests that Mac-2 may promote the development of cancer [23]. Thus, the significant possible explanation for the occurrence of HCC development in patients with elevated M2BPGi levels could be the biological activities of M2BPGi that are mediated by Mac-2.

CONCLUSIONS

In the HCV cohort, M2BPGi can be utilized to predict HCC. To evaluate M2BPGi as a more comprehensive HCC biomarker in patient populations, including those with severe hepatic fibrosis burdens and a wider range of liver diseases, more research is required.

Conflict of Interest: None

Financial Disclosures: None

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